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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 20 1995

James J. Schumann, Esq.
FITCH, EVEN, TABIN & FLANNERY for
THE SALK INSTITUTE FOR BIOLOGICAL STUDIES
4250 Executive Square, Suite 510
La Jolla, CA 92037

Re: Docket No. 92E-0133

Dear Mr. Schumann:

This is in response to your petition for reconsideration of the date of the beginning of the testing phase for Supprelin, as stated in the June 2, 1992 Federal Register Notice (57 Fed. Reg. 23,237), submitted on behalf of The Salk Institute for Biological Studies. On July 16, 1992, you submitted a request for redetermination of this same date. The request was denied by the Associate Commissioner for Health Affairs in a letter dated March 8, 1994.

The petition for reconsideration again asks FDA to use a later investigational new drug application (IND), rather than the one identified by the agency, for purposes of determining the date of the beginning of the testing phase of Supprelin for patent term restoration. We are denying your petition for reconsideration for the reasons stated in this letter.

The petition for reconsideration argues that the testing phase for Supprelin began on the day an existing IND (IND 13,353) was modified to permit use of the active ingredient in Supprelin, histrelin acetate ("histrelin"), for the indicated use of precocious puberty. The petition for reconsideration claims that the later studies using histrelin for precocious puberty constituted the pertinent investigational work with respect to the approved use for Supprelin and that an earlier IND (IND 23,307) that used histrelin for endometriosis, which was also conducted by different investigators than the IND used for precocious puberty, was not relevant with respect to the use of histrelin for precocious puberty. However, your July 16, 1992 request for redetermination acknowledged that the clinical investigators involved in the histrelin study for precocious puberty were authorized to incorporate by reference the earlier IND for purposes of chemistry, toxicology and similar information. As we pointed out in our March 8, 1994 response to your request for redetermination, FDA considers this information material to the approval of Supprelin, and it is for this reason that the date of the earlier IND has been used. Your petition for reconsideration does not address this point at all.

The petition asserts that FDA has decided to formulate an overall procedure to be followed in all multiple IND situations to avoid making individual determinations based on an assessment in each case. It is correct that, in general, with multiple INDs, FDA has used the first IND of the active ingredient of the drug product as the beginning of the testing phase, if information derived from this first IND was or could have been relied on or was relevant for approval to

market the drug product. This is in accord with the explanation provided in the preamble to the final regulation (53 Fed. Reg. 7,298; Monday, March 7 , 1988) which states:

> For drugs for which more than one exemption is in effect, the provisions of the patent extension statute specifically state that the testing phase for human drug products begins on the date an exemption "under subsection (i) of section 505 or subsection (d) of section 507 became effective for the approved human drug product" (35 U.S.C. 156(g)(B)(i)). Thus, while the drug's dosage form and strength during the IND phase need not be identical to that of the approved drug product, the information from the IND studies must have been material to the approval of the drug product. Where multiple INDs are in effect, the agency will consider the testing phase to have begun when the first IND for the approved human drug product became effective.
> (53 Fed. Reg. 7,301)

While the preamble utilized the example of different dosage forms and strengths, the explanation applies to other differences as well, including INDs involving different indications. This is because so many changes may occur in the development of a product as investigational work continues.

However, it should be recognized that FDA does make individual assessments of each case. FDA did review the new drug application (NDA) for Supprelin (NDA 19-836), as well as the information derived from the earlier IND (IND 23,307) for histrelin, and found that the pharmacological review and the chemistry and manufacturing controls sections of the review of the NDA for Supprelin (NDA 19-836) analyzed data derived from information found in the earlier IND (IND 23,307). These included the preclinical animal studies of histrelin, as well as analyses of the drug substance, e.g., an amino acid composition, stability information and physical/chemical characteristics. Therefore, it is apparent that the agency did consider the information material, and the appropriate beginning of the testing phase for Supprelin is the date of the first IND (IND 23,307) for its active ingredient, histrelin acetate. This date is February 8, 1984, as stated in the June 2, 1992 Federal Register Notice (57 Fed. Reg. 23,237).

For these reasons, your petition for reconsideration of the beginning of the testing phase for Supprelin is denied.

Sincerely yours,

Sharon Smith Holston

Sharon Smith Holston
Deputy Commissioner
for External Affairs